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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/665,951	09/18/2003	James McSwiggen	MBHB02-742-F (400.131)	8325

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EXAMINER	
BOWMAN, AMY HUDSON	

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 10/02/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/665,951	MCSWIGGEN ET AL.	
	Examiner	Art Unit	
	Amy H. Bowman	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 July 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *36-56* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *36-56* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's response filed 7/6/2006 has been considered. Rejections and/or objections not reiterated from the previous office action mailed 6/21/2006 are hereby withdrawn. The following rejections and/or objections are either newly applied or are reiterated and are the only rejections and/or objections presently applied to the instant application.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 36-56 are pending in the application.

Response to Priority

Applicant points to support for the instant claims in application 60/363,124, filed on 3/11/2002. Thus, the instant application 10/665,951 is accorded an effective filing date of 3/11/2002.

Additionally, applicant points to support for the instant claims on page 55 in application 60/334,461, filed on 11/30/2001. Upon review of page 55 of application 60/334,461, there is no support for a method of cleaving RNA comprising SEQ ID NO: 2460 comprising contacting a siRNA molecule with SEQ ID NO: 2460, wherein each strand of the siRNA comprises about 18 to about 27 nucleotides and the instantly recited modifications.

Thus, the instant application 10/665,951 is accorded an effective filing date of 3/11/2002.

New Objections/Rejections

Declaration

The declaration filed on 4/11/2006 has been considered and is discussed in the "Response to Arguments filed 4/11/2006 considered relevant to instant rejections under 35 USC § 103" section below.

Specification

The disclosure is objected to because of the following informalities: The word "described" is spelled "descrbed" on page 12, line 12 of the specification.

The above mentioned instance is not intended to be an exhaustive list of typographical errors in the disclosure. Applicant is encouraged to review the disclosure for any such errors.

Appropriate correction is required.

Claim Objections

Claim 38 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form.

Claim 38 recites, "wherein the siRNA molecule comprises ribonucleotides". Since this claim is drawn to a siRNA, the molecule by nature comprises ribonucleotides. Therefore, claim 38 fails to further limit claim 36.

Claim 49 is objected to because of the following informalities: Claim 49 does not end with a period. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 36-56 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 36 recites "double-stranded ribonucleic acid (siRNA)". However, "siRNA" is not an abbreviation for "double-stranded ribonucleic acid".

Recitation of "short interfering RNA (siRNA)", for example, would obviate this rejection.

Claims 37-56 are rejected because they depend from claim 36.

Claim 37 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 37 recites, "the siRNA molecule comprises no ribonucleotides." However, since this claim is drawn to a si**RNA**, the molecule by nature comprises ribonucleotides.

Claim 55 recites the limitation "said 2'-deoxy-pyrimidine" in claim 54. However, there is insufficient antecedent basis for this limitation in claim 54. Recitation of "said 2'-deoxy-pyrimidines are 2'-deoxy-thymidines", for example, would obviate this rejection.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 36-56 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of cleaving RNA comprising SEQ ID NO: 2460 encoded by a mammalian VEGFr1 gene comprising contacting a siRNA with the RNA encoded by the VEGFr1 gene *in vitro*, does not reasonably provide enablement for such a method *in vivo*. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims. Specifically, the claims encompass *in vivo* effects that are not enabled.

Factors to be considered in a determination of lack of enablement include, but are not limited to:

(A) The breadth of the claims;

(B) The nature of the invention;

(C) The state of the prior art;

(D) The level of one of ordinary skill;

(E) The level of predictability in the art;

(F) The amount of direction provided by the inventor;

(G) The existence of working examples; and

(H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)

The instant invention is drawn to a method of cleaving RNA comprising SEQ ID NO: 2460 encoded by a mammalian VEGFr1 gene comprising contacting a siRNA molecule with the RNA encoded by the VEGFr1 gene under conditions suitable for the cleavage of RNA, wherein each strand comprises about 18 to about 27 nucleotides and one or more chemical modifications, and one of the strands is complementary to RNA encoded by mammalian VEGFr1 gene and the other strand is complementary to the first strand. The invention is further drawn to modifications to the dsRNA molecule, terminal cap moieties, and 3' overhangs.

The specification teaches ocular injection of a siNA molecule in mice, as well as several other prophetic examples.

There is no guidance in the specification as filed that teaches how to cleave RNA comprising SEQ ID NO: 2460 encoded by a mammalian VEGFr1 gene via contacting a siRNA with the RNA encoded by the VEGFr1 gene via any other means than ocular injection *in vivo*. Although applicant has demonstrated delivery via ocular injection in mice *in vivo*, applicant is not enabled for delivery of a siRNA *in vivo* by the broadly

recited methods, as delivery is known in the art to be unpredictable with regards to dsRNA duplexes.

The references cited herein illustrate the state of the art for therapeutic *in vivo* applications using dsRNA. Scherer et al. (Nat. Biotechnol., 2003, 21(12), pages 1457-1465) teach that antisense oligonucleotides (ODNs), ribozymes, DNAzymes and RNA interference (RNAi) each face remarkably similar problems for effective application: efficient delivery, enhanced stability, minimization of off-target effects and identification of sensitive sites in the target RNAs. Scherer et al. teach that these challenges have been in existence from the first attempts to use antisense research tools, and need to be met before any antisense molecule can become widely accepted as a therapeutic agent.

Mahato et al. (Expert Opinion on Drug Delivery, January 2005, Vol. 2, No. 1, pages 3-28) teach that antisense oligodeoxynucleotides and double-stranded small interfering RNAs have great potential for the treatment of many severe and debilitating diseases. Mahato et al. teach that efforts have made significant progress in turning these nucleic acid drugs into therapeutics, and there is already one FDA-approved antisense drug in the clinic. Mahato et al. teach that despite the success of one product and several other ongoing clinical trials, challenges still exist in their stability, cellular uptake, disposition, site-specific delivery and therapeutic efficacy. Mahato et al. teach that in order for siRNAs to be used as therapeutic molecules several problems have to be overcome, including: the selection of the best sequence-specific siRNA for the gene to be targeted and the ability to minimize degradation in the body fluids and tissues.

The post-filing art of Zhang et al. (Current Pharmaceutical Biotechnology 2004, vol. 5, p.1-7) reviews the state of the art with regard to RNAi and has this to say about use in mammalian cells. "Use of siRNA in mammalian cells could be just as far-reaching, with the applications extending to functional genomics and therapeutics. But various technical issues must be addressed, especially for large-scale applications. For instance, dsRNA can be delivered to *C. elegans* by feeding or soaking, but effective delivery of siRNAs to mammalian cells will not be so simple."

As outlined above, it is well known that there is a high level of unpredictability in the dsRNA art for therapeutic *in vivo* applications. The scope of the claims in view of the specification as filed together do not reconcile the unpredictability in the art to enable one of skill in the art to make and/or use the claimed invention, namely a broad method of cleaving RNA encompassing *in vivo* effects via any means of delivery.

Given the teachings of the specification as discussed above, one skilled in the art could not predict *a priori* whether introduction of dsRNA *in vivo* by the broadly disclosed methodologies of the instantly claimed invention, would result in successful cleavage. To practice the claimed invention, one of skill in the art would have to *de novo* determine; the stability of the molecule *in vivo*, delivery of the molecule to the whole organism, specificity to the target tissue *in vivo*, dosage and toxicity *in vivo*, and entry of the molecule into the cell *in vivo* and the effective action therein. Without further guidance, one of skill in the art would have to practice a substantial amount of trial and error experimentation, an amount considered undue and not routine, to practice the instantly claimed invention.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 36-40 and 44-55 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pavco et al. (US 6,346,398 B1), in view of Elbashir et al. (The EMBO Journal, Vol. 20, No. 23, pp. 6877-6888, 2001), Parrish et al. (Molecular Cell, Vol. 6, pp. 1077-1087, 2000), Cook et al. (US 5,587,471), Hammond et al. (Nature, 2001, Vol. 2, pages 110-119), and Caplen (Expert Opin Biol Ther, 2003 Jul, 3(4), pp. 575-86).

The instant invention is drawn to a method of cleaving RNA comprising SEQ ID NO: 2460 encoded by a mammalian VEGFr1 gene comprising contacting a siRNA molecule with the RNA encoded by the VEGFr1 gene under conditions suitable for the cleavage of RNA, wherein each strand comprises about 18 to about 27 nucleotides and one or more chemical modifications, and one of the strands is complementary to RNA encoded by mammalian VEGFr1 gene and the other strand is complementary to the first strand. The invention is drawn to modifications to the dsRNA molecule, terminal cap moieties, and 3' overhangs.

Pavco et al. teach hammerhead ribozymes and antisense oligonucleotides targeted to flt-1, another name for the instantly recited target. Pavco et al. teach chemical modifications including 2'-O-methyl modifications, phosphorothioates, and

inverted abasic deoxyribose. Pavco et al. teach that flt-1 is one of the most abundant VEGF receptors and that VEGF expression has been associated with several pathological states such as tumor angiogenesis and rheumatoid arthritis. Pavco et al. teach that targeting and inhibiting flt-1 would beneficially decrease VEGF expression since VEGF exerts its influence by binding to cell surface receptors.

Elbashir et al. teach dsRNA duplexes 21-23 nucleotides in length with 2 nt 3' overhangs, wherein the overhangs are 2'-deoxy-thymidines. Elbashir et al. teach duplexes with 3' overhangs, as well as duplexes with blunt ends wherein the sense and antisense strand are 100% complementary (see figure 1). Elbashir et al. teach 2'-deoxy and 2'-O-methyl modifications to one or both strands. Elbashir et al. teach that modifications are tolerated depending on the location in the duplex. Elbashir et al. teach that substitution of the 2 nt 3' overhangs by 2'-deoxynucleotides had no effect and even the replacement by two additional ribonucleotides by 2'-deoxyribonucleotides adjacent to the overhangs in the paired region produced significantly active siRNAs. Elbashir et al. teach complete substitution of one or both strands of the siRNA duplex, wherein the completely substituted duplex is considered to comprise no ribonucleotides.

Parrish et al. teach 26 bp siRNA duplexes that mediate RNAi. Parrish et al. teach modified double stranded RNA molecules comprising a first nucleotide sequence with complementarity to a target and a second nucleotide sequence with complementarity to said first nucleotide sequence. One or both strands comprise modifications. Each strand of the dsRNA molecules taught by Parrish et al. comprises about 18 to about 27 nucleotides, more specifically 26 nucleotides or longer. Parrish et

al. teach that certain modifications were well tolerated on the sense, but not the antisense strand, indicating that the two trigger strands have distinct roles in the interference process (see summary). Parrish et al. teach 2'-deoxy-2'-fluoro pyrimidine modifications in the sense or antisense strand (see figure 5). Although Parrish et al. is being relied upon for the teaching of chemical modifications to long dsRNA, the long dsRNA of Parrish et al. was necessarily cleaved into modified siRNA duplexes. Furthermore, the instant claim language is open and embraces longer fragments.

Cook et al. teach various conjugates and modifications that can be incorporated into oligonucleotides to improve the pharmacokinetic properties of an oligonucleotide, including glyceryl (see columns 2 and 3).

Hammond et al. teach two methods for silencing specific genes, antisense and RNA interference. Hammond et al. teach that although antisense methods are straightforward techniques for probing gene function, the methods have suffered from questionable specificity and incomplete efficacy (see page 110, column 1). Hammond et al. teach that dsRNAs have been shown to inhibit gene expression in a sequence-specific manner and that RNAi is a potent method, requiring only a few molecules of dsRNA per cell to silence expression.

It would have been obvious to cleave RNA encoded by a mammalian VEGFr1 gene (SEQ ID NO: 2460) with a siRNA because ribozymes and antisense oligos had been previously successfully targeted to the same gene to decrease VEGF expression, as taught by Pavco et al. It would have been obvious to substitute a siRNA duplex, as

taught by Elbashir et al. and Parrish et al, for the antisense oligonucleotide or ribozyme taught by Pavco et al.

Furthermore, it would have been obvious to modify the dsRNA duplexes with 2'-O-methyl modifications, phosphorothioates, and inverted abasic deoxyribose, as taught by Pavco et al., 2'-deoxy and 2'-O-methyl modifications to one or both strands, as well as 3' overhangs of 2'-deoxy-thymidines, as taught by Elbashir et al., 2'-deoxy-2'-fluoro modifications, as taught by Parrish et al., and glyceryl modifications, as taught by Cook et al.

One would have been motivated to use a siRNA targeted to VEGFr1 comprising SEQ ID NO: 2460 instead of an antisense oligonucleotide or ribozymes, as taught by Pavco et al. because Hammond et al. teach that using dsRNA to inhibit gene expression is a sequence specific and potent method, requiring only a few molecules of dsRNA per cell to inhibit the expression of a target gene. Pavco et al. teach inhibition of the instantly recited target and it was known in the art at the time the invention was made that using siRNA duplexes instead of antisense oligonucleotides is preferred, as evidenced by Hammond et al.

Additionally, one would have been motivated to incorporate each of the above mentioned modifications, since each of the modifications were known to enhance the activity of sequence specific inhibitors of target gene expression. The modifications were each known in the art, as evidenced by the modified antisense oligonucleotides and ribozymes taught by Pavco et al., modified siRNA duplexes taught by Elbashir et al. and Parrish et al., and modified oligonucleotides taught by Cook et al. One would be

motivated to maximize a double stranded nucleic acid by incorporating each of the modifications that were known in the art. Elbashir et al. and Parrish et al. each teach combinations of modifications to duplexes and teach that different modifications are tolerated at different locations of the duplex. One would be motivated to test modifications that are known to benefit oligonucleotide delivery and apply each of them to a dsRNA duplex in order to optimize delivery of the duplex.

Although each of the compounds cited are not specifically siRNA duplexes, each of these molecules were known to face the same delivery challenges. Further support for this is offered by Caplen, who points out that, "Many of the problems associated with developing RNAi as an effective therapeutic are the same as encountered with previous gene therapy approaches. The key issues of delivering nucleic acids to the required tissue and cell type, while ensuring an appropriate level of efficacy with minimum toxicity induced by the vector system..." (see page 581). As evidenced by Caplen, RNA interference encounters similar problems as other nucleic acid based therapies, and therefore, supports the examiner's position that one would be motivated to incorporate each of the instant modifications in an attempt to enhance delivery of any of the sequence specific oligonucleotide therapeutics.

Finally, one would have a reasonable expectation of success given that each of the modifications were known in the art at the time the invention was made to add benefits to oligonucleotides. One would expect for such modifications to benefit siRNA duplexes, as each had shown to benefit either siRNA duplexes or other oligonucleotides such as antisense oligonucleotides or ribozymes. One would have a reasonable

expectation of success to specifically target a mammalian VEGFr1 comprising SEQ ID NO: 2460 with a siRNA because it was known in the art that this gene could be successfully inhibited with oligonucleotides, as evidenced by Pavco et al. and that siRNA duplexes are preferred inhibitory molecules, as evidenced by Hammond et al.

Thus in the absence of evidence to the contrary, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made.

Claims 36-55 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pavco et al. (US 6,346,398 B1), in view of Elbashir et al. (The EMBO Journal, Vol. 20, No. 23, pp. 6877-6888, 2001), Parrish et al. (Molecular Cell, Vol. 6, pp. 1077-1087, 2000), Cook et al. (US 5,587,471), Hammond et al. (Nature, 2001, Vol. 2, pages 110-119), and Caplen (Expert Opin Biol Ther, 2003 Jul, 3(4), pp. 575-86), as explained above, further in view of Agrawal et al. (WO 94/01550).

The instant invention is drawn to a method of cleaving RNA comprising SEQ ID NO: 2460 encoded by a mammalian VEGFr1 gene comprising contacting a siRNA molecule with the RNA encoded by the VEGFr1 gene under conditions suitable for the cleavage of RNA, wherein each strand comprises about 18 to about 27 nucleotides and one or more chemical modifications, and one of the strands is complementary to RNA encoded by mammalian VEGFr1 gene and the other strand is complementary to the first strand. The invention is drawn to modifications to the dsRNA molecule, terminal cap moieties, linkers, and 3' overhangs.

Pavco et al. do not teach polynucleotide or non-nucleotide linkers.

Agrawal et al. teach self-stabilized oligonucleotides comprising a sense strand and an antisense strand connected via a polynucleotide linker (see figure 5, 3rd molecule, for example). Agrawal et al. teach that the oligonucleotide forms a totally or partially double-stranded hairpin structure that is resistant to nucleolytic degradation (see page 5) and that preferably the complementary region is about 50 nucleotides or less (see page 15), which would form a duplex of 25 base pairs or less. The oligonucleotides can be polymers of ribonucleotides or deoxyribonucleotides and can have a nucleotide or non-nucleotide linker (see page 15). Agrawal et al. teach phosphorothioate and 2'-O-methyl modifications. Agrawal et al. teach that such modifications increase stabilization and resistance to nucleolytic degradation without the disadvantages of oligonucleotides that are known in the art (see page 3 and 16).

It would have been obvious to one of ordinary skill in the art to incorporate polynucleotide or non-nucleotide linkers, as taught by Agrawal et al., into a siRNA molecule targeted to VEGFr1 (SEQ ID NO: 2460), as explained in the 35 U.S.C. 103(a) rejection above.

One would have been motivated to incorporate nucleotide or non-nucleotide linkers into the siRNA because Agrawal et al. teach hairpin formations that increase stabilization and resistance to nucleolytic degradation.

Finally, one would have a reasonable expectation of success given that linkers were known in the art at the time the invention was made to increase stabilization of double-stranded oligonucleotides, as evidenced by Agrawal et al.

Thus in the absence of evidence to the contrary, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made.

Response to Arguments filed 4/11/2006 considered relevant to instant rejections under 35 USC § 103

Applicant argues that Elbashir et al. teach siRNA technology generally, but fails to teach, mention, or suggest double stranded nucleic acid molecules as presently claimed by virtue of chemical modifications and the VEGFr1 target sequence recited. It is noted that Elbashir et al. is not relied upon for teaching anything specific to VEGFr1, but rather for teaching siRNA technology and modifications of siRNA duplexes, which is considered integral to the instant invention.

Applicant argues that Parrish et al. report that duplexes as short as 26 bp can trigger RNAi, however Parrish deals with non-mammalian systems and that Parrish reports that dsRNA triggers having 14 and 23 uninterrupted nucleotide identity to the target induced no interference. Additionally, Parrish shows that certain chemical modifications are tolerated in long dsRNA, but that Elbashir did not gain useful knowledge from Parrish to allow successful modification of siRNAs as instantly claimed. It is noted that arguments regarding the thought process of Elbashir et al. are not considered relevant to the instant argument and will not be discussed. The examiner is strictly relying upon the teaching of each piece of prior art.

It is significant that both Elbashir et al. and Parrish et al. teach siRNA duplexes

within the instantly recited size range that induce target cleavage and that Elbashir et al. and Parrish et al. each teach chemically modifying dsRNA with instantly recited modifications. Additionally, applicant is arguing a limitation that is not in the claims regarding Parrish teaching long dsRNA because the instant claims recite open language that embrace long dsRNAs.

As additional response to the applicant's position that Parrish et al. only teach long dsRNA molecules that are modified, it is now known that the long dsRNA molecules of Parrish et al. would have necessarily been cleaved to shorter modified dsRNA duplexes. Inherent anticipation does not require recognition in the prior art (see MPEP 2112 and *Schering Corp. v. Geneva Pharm. Inc.*, 339 F.3d 1373, 1377, 67USPQ2d 1664, 1668 (Fed. Cir. 2003)).

Applicant argues that Pavco et al. and Cook teach non-analogous art, specifically ribozymes and antisense. On the contrary, as explained in the 35 USC § 103 rejections above, ribozymes and antisense are certainly not considered non-analogous art. Each of the compounds relied upon by the examiner were known in the art to be sequence specific mediators of target gene expression, each based upon recognition of an antisense strand, and each known to face the same delivery challenges. Braasch et al. specifically teach that chemical modifications are needed to overcome such problems.

Applicant argues that Elbashir failed in arriving at siRNAs with modifications beyond replacement of the 3'-terminal nucleotides. Again, applicant is arguing limitations that are not in the instant claims. Elbashir et al. teaches chemical modifications and resultant successful target inhibition. Instant claim 36 requires each

strand to comprise one or more chemical modifications selected from the group consisting of 2'-O-methyl, 2'-deoxy-2'-fluoro, and 2'-deoxy. Certainly Elbashir et al. does not teach away from each strand comprising one or more of such chemical modifications.

Importantly, it is noted that Elbashir et al. teach that 100% modification of one or both strands of a siRNA duplex specifically with 2'-O-methyl or 2'-deoxy modifications abolishes activity. Therefore, Elbashir et al. does not teach away from modification with 2'-O-methyl, 2'-deoxy, or other modifications at percentages less than 100% of one or both strands. Furthermore, Elbashir et al. does not teach away from modification at any percentage with modifications other than 2'-O-methyl or 2'-deoxy modifications. Although Elbashir et al. teach that modification of 100% of the duplex with 2'-deoxy or 2-O-methyl modifications abolished activity, one of skill in the art would certainly be motivated to modify at percentages less than 100%, as Elbashir does teach successful inhibition with duplexes modified at less than 100% of the nucleotide positions. Furthermore, each of the specific modifications were known in the art to benefit oligonucleotide delivery to cells.

Applicant argues that the examiner's position goes no further than suggesting that it would be obvious to try targeting VEGFr1 with such molecules. On the contrary, as explained in the 35 USC § 103 rejections above, it was known in the art to inhibit the instantly recited target with antisense therapeutics including antisense oligonucleotides and ribozymes. It was known in the art that siRNA duplexes are potent and preferable inhibitors compared to previous oligonucleotide inhibitors. Certainly it would have been

obvious to one of ordinary skill in the art to utilize a siRNA directed to a target that has already been inhibited with other antisense agents.

With regards to the Declaration under 37 C.F.R. 1.132 filed 4/11/2006, applicant focuses on the significant structural differences between long double stranded RNA, antisense oligonucleotides, ribozymes, and siRNAs. As explained above, the examiner is not arguing the structural differences between each of these molecules but is simply relying on art within the oligonucleotide therapeutic field regarding chemical modifications that aid in the stability and delivery of oligonucleotides, each of which are problems for dsRNA, antisense oligonucleotides, and ribozymes.

Applicant further asserts that the relatively high potency of siRNAs, suggested at the time that no additional stability-inducing modifications would be necessary. Contrary to applicant's assertion, chemical modifications were known in the art to be beneficial to oligonucleotide therapeutics, including siRNA duplexes, as demonstrated by Elbashir et al. (EMBO) and long dsRNA, as evidenced by Parrish et al., which would necessarily be cleaved to smaller fragments, as explained above. Even post-filing, it is still acknowledged that siRNAs face the same delivery challenges as other oligonucleotide gene therapy approaches, as evidenced by Scherer et al. and Caplen above.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP

§ 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Amy H. Bowman whose telephone number is (571) 272-0755.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on (571) 272-4517. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

AHB

JAMES SCHULTZ, PH.D.
PRIMARY EXAMINER